PB88-233952

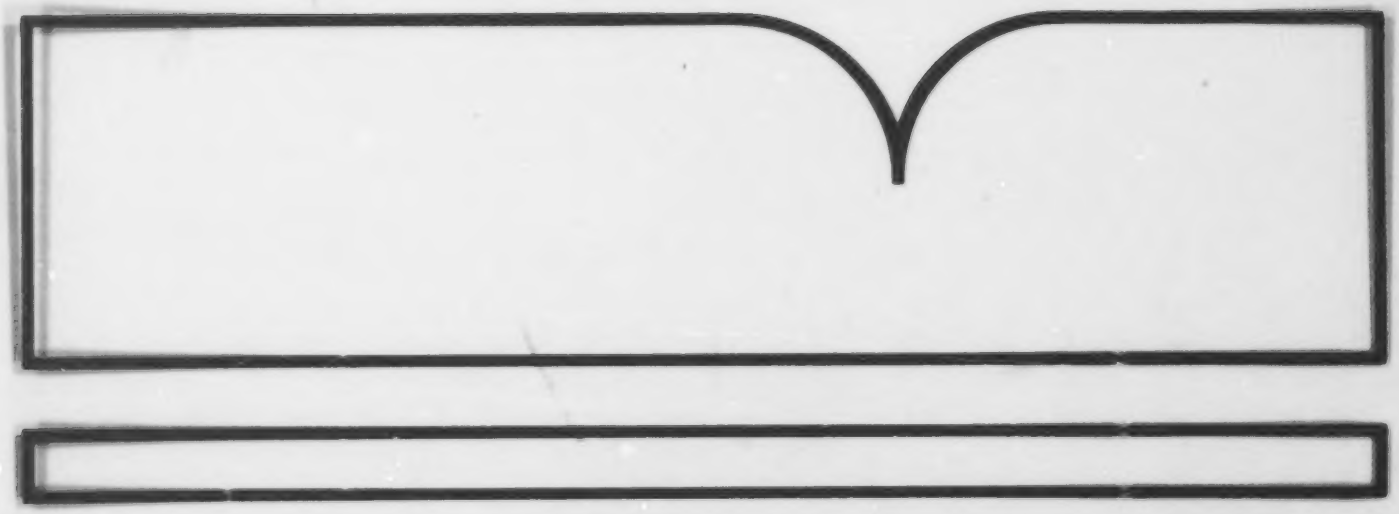
Factors to Be Considered in a Dosimetry Model for Risk Assessment of Inhaled Particles

Salzburg Univ. (Austria)

Prepared for

Health Effects Research Lab.
Research Triangle Park, NC

1986



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completi

1. REPORT NO. EPA/600/J-86/469	2.	3. PB88-233952
4. TITLE AND SUBTITLE Factors to be Considered in a Dosimetry Model for Risk Assessment of Inhaled Particles (Journal Version)		5. REPORT DATE 1986 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) T. Martonen * W. Hofmann **		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS EPA,HERL,ITD,TB, MD-82 * RTP, NC 27711 University of Salzburg, ** Austria		10. PROGRAM ELEMENT NO. AAGA1D 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Research & Development Health Effects Research Laboratory USEPA Research Triangle Park, NC 27711		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE EPA-600/11

15. SUPPLEMENTARY NOTES

Radiation Protection Dosimetry, vol. 15, No. 4, pp. 225-232 (1986)

16. ABSTRACT

Clinical findings suggest that bronchogenic tumors have a predilection for certain airway locations in man. Aerosol deposition studies with laryngeal-tracheobronchial casts and models indicate that such sites in situ correspond to "hot spots" of deposition, and that cells located at carinal ridges may be particularly susceptible to development of bronchial carcinomas. For cigarette smokers, the etiology of lung cancer may be affected by synergistic interactions following exposures to naturally occurring indoor radon progeny. The problem is exacerbated for workers in the uranium mining and milling industry due to additional exposures to radioactive dust particles. This paper suggests that heterogeneous local deposition patterns in bronchial airways, concomitant with increased radiation exposure to targeted cells, may be the relevant factor in lung cancer induction, and implies that enhanced activity sites should be accounted for in risk assessment carcinogenesis models.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS (This Report) UNCLASSIFIED 20. SECURITY CLASS (This page) UNCLASSIFIED	21. NO. OF PAGES 10 22. PRICE PC $9.95/A2 $6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA/600/J-86/469
JOURNAL ARTICLE

Radiation Protection Dosimetry
Vol. 15 No. 4 pp. 225–232 (1986)
Nuclear Technology Publishing

FACTORS TO BE CONSIDERED IN A DOSIMETRY MODEL FOR RISK ASSESSMENT OF INHALED PARTICLES

T. Martonen* and W. Hofmann†
*Inhalation Toxicology Division, Health Effects Research Laboratory
US Environmental Protection Agency, Research Triangle Park, NC 27711, USA
†Abteilung für Biophysik, Universität Salzburg
A-5020 Salzburg, Austria

Received May 2 1985, Amended August 5 1986, Accepted August 12 1986

Abstract — Clinical findings suggest that bronchogenic tumours have a predilection for certain airway locations in man. Aerosol deposition studies with laryngeal-tracheobronchial casts and models indicate that such sites *in situ* correspond to 'hot spots' of deposition, and that cells located at carinal ridges may be particularly susceptible to development of bronchial carcinomas. For cigarette smokers, the aetiology of lung cancer may be affected by synergistic interactions following exposures to naturally occurring indoor radon progeny. The problem is exacerbated for workers in the uranium mining and milling industry due to additional exposures to radioactive dust particles. This paper suggests that heterogeneous local deposition patterns in bronchial airways, concomitant with increased radiation exposure to targeted cells, may be the relevant factor in lung cancer induction, and implies that enhanced activity sites should be accounted for in risk assessment carcinogenesis models.

INTRODUCTION

Personnel in uranium mining and milling operations may be exposed to airborne particulate matter containing radionuclides that are alpha emitters. Epidemiological studies have documented high incidences of lung carcinomas among workers exposed to high levels of ^{222}Rn[1,2] and cigarette smokers[3]. To assess the potential health hazards following inhalation exposure to such materials, scientists must know not only the total mass of particulate material deposited but its intercompartmental regional distribution as well, because different compartments of the respiratory tract have clearance mechanisms that differ in effectiveness and rate. Indeed, the high incidences of bronchial carcinomas at selective locations within the tracheobronchial (TB) tree[4] suggest that it may also be necessary to know the intracompartmental dispersion pattern of a given total compartmental dose.

To aid in the development of a dosimetry model suitable for estimating hazards to human health posed by inhalation of ambient radionuclides and cigarette smoke, we reviewed data from a selected series of experimental studies measuring aerosol deposition efficiencies in surrogate systems of the human respiratory tract. Our report focuses upon aerosol deposition experiments conducted with replica TB casts or models that are placed downstream from replica laryngeal casts or suitable surrogates. The importance of the latter is evidenced in that they are necessary to produce physiologically realistic airflow patterns within the trachea and large bronchial airways, that is, the laryngeal jet and larynx-induced flow instabilities. The effects of the laryngeal jet upon airstream behaviour have been noted by Owen[5], and its influences upon particle trajectories in the trachea quantified by Chan *et al*[6,7]. Moreover, deposition measurements made in a replica TB cast with and without a replica laryngeal cast have specifically quantified the extent to which larynx-induced effects control the distribution of large particles in upper bronchial airways[8].

AEROSOL DISTRIBUTION PATTERNS

To facilitate a comparison of data from various studies, it will be necessary to adopt an idealised airway branching scheme as a basis for definition of terminology. We shall assume a dichotomous branching mode where the trachea and main, lobar, segmental and first generation of subsegmental bronchi, etc., are airway generations I = 0, 1, 2, 3, 4, etc., respectively. In common parlance an airway of generation I is a 'parent' to two 'daughter' airways of the succeeding generation I + 1. Here, for the purpose of measuring relative aerosol deposition efficiencies, we subdivide the two daughter airways into three geometrical components: a bifurcation zone (which contains the airstream divider, or carina) and two distal (to the carina) tubular segments.

Schlesinger *et al*[9] quantified the deposition of monodisperse, iron oxide (^{99m}Tc-tagged) aerosols in combined replica laryngeal and TB casts. The latter

NTIS is authorized to reproduce and sell this report. Permission for further reproduction must be obtained from the copyright owner.

were made from solid wax master casts pruned to bronchioles no smaller than 2 mm in diameter. The surrogate larynges, modelled from a cadaveric larynx, had internal configurations related to constant respiratory flow rates of 15, 30, and 60 l.min^{-1}. Aerosols had mass median aerodynamic diameters (MMADs) between 2.6 μm and 8.0 μm. Bifurcation zone deposition efficiencies, B_d, defined as

$$B_d = \frac{\left\{\frac{\text{bifurcation zone aerosol mass}}{\text{daughter airways total† aerosol mass}}\right\}}{\left\{\frac{\text{bifurcation zone surface area}}{\text{daughter airways total† surface area}}\right\}}$$

were reported as being minimum at the trachea to main bronchi transition, and maximum entering the segmental bronchi († denotes that the quantity is bifurcation zone inclusive). In a later, comparable study, Schlesinger *et al*[10] also measured enhanced deposition at bifurcations by using aerosols with MMADs between 2.5 μm and 8.1 μm. Data from the two works are summarised in Table 1. In a subsequent work[11] preferential deposition at airway branching locations was expressed as a function of the five distinct lobar positions in the human lung, and the authors related enhanced aerosol deposition at bifurcation regions to clinically observed incidences of bronchogenic carcinomas.

Martonen[12] and Martonen and Lowe[13] measured the selective deposition of aerosols in combined single pathway TB models and replica laryngeal casts. Monodisperse ammonium fluorescein aerosols had MMADs between 1.9 μm and 10.6 μm. Aerosol sampling rates through the TB models were constant (either 15, 30, or 60 l.min^{-1}) with appropriate flow-specific laryngeal casts in place. Bifurcation deposition efficiencies reported in the two studies are presented in Table 2. The pattern of deposition at bronchial bifurcations (i.e. minimum entering main bronchi (generation 1), maximum at segmental bronchi (generation 3)) among the airways of the single pathway TB models is the same as the pattern observed with the aforementioned replica TB cast experiments. Distribution of deposited material within bifurcation zones was very heterogeneous, as was observed by dissecting a TB model in the sagittal plane. The extent to which particles are concentrated at carinal ridges is clearly shown in Figure 1. Greatly enhanced particle collection at 'dividing spurs' within a replica TB cast has been quantified for a particle size of 6 μm at a flow rate of 30 l.min^{-1} [8].

Although enhanced deposition of large particles may be expected *a priori* at large airway branching sites because of the inertial impaction mechanism, preferential deposition of submicron particles has also been reported. The quantitative data of Schlesinger *et al*[9] and Schlesinger and Lippmann[11] for monodisperse, ^{99m}Tc-labelled iron oxide aerosols deposited at airway bifurcations within combined replica laryngeal-multigeneration bronchial casts of man are given in Table 3. Regarding the deposition of naturally occurring radionuclides, Chamberlain and Dyson[14] have detected enhanced deposition of short-lived disintegration products of radon and

Table 1. Bifurcation zone deposition efficiencies within human replica TB casts (Schlesinger *et al*[9,10]).

Airway generation	15 l.min^{-1}						30 l.min^{-1}			60 l.min^{-1}					
	3.0μm	3.1μm	4.2μm	4.4μm	7.0μm	7.1μm	2.8μm	5.2μm	7.7μm	2.5μm	2.6μm	4.4μm	4.8μm	8.0μm	8.1μm
1	0.28	0.67	0.51	0.80	0.87	0.80	0.09	0.25	1.06	0.57	1.33	0.52	1.07	1.60	0.76
2	1.15	2.73	1.06	1.73	2.47	0.95	1.42	1.04	0.78	0.67	2.80	1.46	1.40	3.33	1.47
3	1.68	2.07	2.99	2.33	2.93	2.31	3.08	2.73	3.06	1.87	1.93	1.91	2.07	4.53	1.78
4	1.16	1.20	1.64	1.80	1.87	1.75	1.24	1.48	1.97	1.54	2.00	1.65	2.13	2.40	1.65
5	1.06	—	1.09	—	—	1.00	1.11	1.05	1.37	1.12	—	1.98	—	—	1.20
6	0.77	—	0.99	—	—	1.03	1.17	1.05	1.10	1.34	—	1.27	—	—	0.98

Table 2. Bifurcation zone deposition efficiencies within human single pathway TB models (Martonen[12]; Martonen and Lowe[13]).

Airway generation	15 l.min^{-1}				30 l.min^{-1}			60 l.min^{-1}			
	1.9μm	2.1μm	3.0μm	6.7μm	3.3μm	3.6μm	6.8μm	1.9μm	6.1μm	8.7μm	10.6μm
1	0.80	0.42	0.51	0.83	0.17	0.25	0.65	0.50	0.84	1.01	1.20
2	1.15	1.08	1.15	0.92	1.08	1.19	1.35	1.30	1.14	1.40	1.52
3	1.50	1.38	1.62	1.36	2.29	1.83	2.31	1.93	1.84	3.05	3.16
4	0.91	0.90	0.87	1.12	1.34	1.47	1.57	1.74	1.46	2.10	1.94
5	1.10	0.85	0.91	1.18	1.48	1.63	1.50	1.63	1.78	1.75	1.60

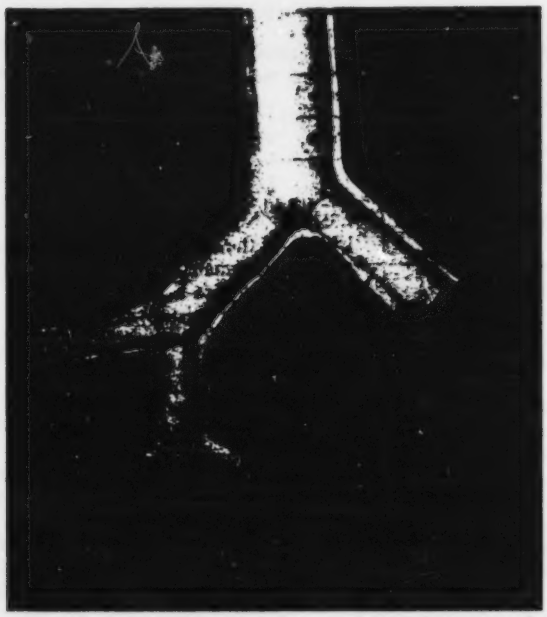


Figure 1. Sagittal section of a single pathway model of the trachea and upper bronchial airways showing the deposition pattern of a monodisperse ammonium fluorescein aerosol. Aerodynamic particle size is 6.8 μm; flow rate is 30 l.min^{-1} (see Table 2).

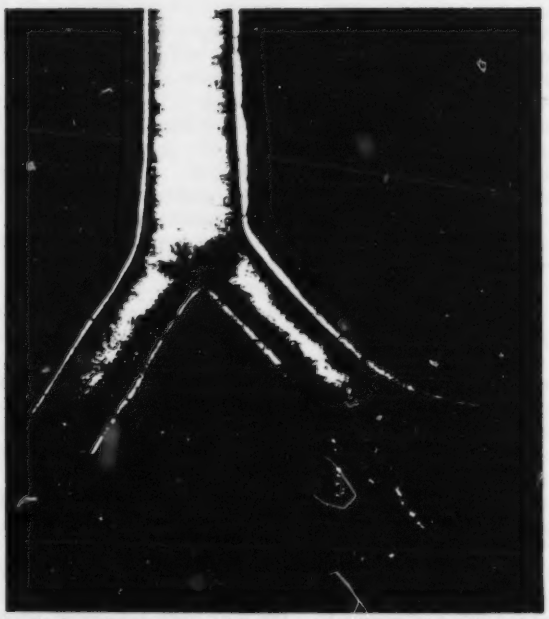


Figure 2. Sagittal section of a single pathway model of the trachea and upper bronchial airways showing the deposition pattern of an undiluted, polydisperse cigarette smoke aerosol.

Table 3. Submicron particle bifurcation zone deposition efficiencies within human replica TB casts (Schlesinger *et al*[9]; Schlesinger and Lippmann[11]).

Airway generation	15 l.min^{-1}		30 l.min^{-1}
	0.28μm	0.28μm	0.26μm
1	0.47	0.61	0.82
2	2.67	3.22	2.12
3	2.13	1.50	1.35
4	0.87	0.94	1.12

thoron within the bifurcation zone of a human replica tracheal-main bronchial cast. Enhanced deposition may be attributed to the action of the diffusion mechanism in a non-laminar airstream[15]. (Note: The experimental data of Martin and Jacobi[16] quantifying the deposition of a radon decay product (^{212}Pb) within plastic TB models are also consistent with theoretically predicted submicron particle behaviour in non-laminar airflow. Although the latter study did not use a laryngeal cast or surrogate proximal to the model airways, and, consequently, the airflow pattern may not have been a correct simulation of *in vivo* conditions, by experimental design the airflow pattern was nonetheless non-laminar.)

Deposition patterns of cigarette smoke have been examined in the combined replica laryngeal cast-single pathway TB model systems[17]. The smoke is polydisperse, consisting of particulate matter with aerodynamic diameters (D_{aes}) in the 0.1 μm to 1.0 μm range[18]. Figure 2 shows a TB model cut in a sagittal plane to view the cigarette smoke deposition pattern for a flow rate of 30 l.min^{-1}. Three major observations can be made concerning smoke dispersion among the bronchial passages: (1) deposition was enhanced at airway branching regions in comparison to tubular segments; (2) highly concentrated deposits were found within airway bifurcations at carinal ridges; (3) deposited cigarette smoke particles were non-uniformly distributed within tubular airway segments (deposition was enhanced along posterior airway walls).

It should be noted that Figures 1 and 2 differ in two major respects. In Figure 1, particles are large and aerosols are monodisperse. In Figure 2, particles are small and aerosols are polydisperse. A striking common feature, however, is that carinal ridges are sites of concentrated deposits.

Limited data are available quantifying particle dynamics in non-steady flow through branching networks. A comparison of particle deposition patterns within replica bronchial passages for constant versus cyclic inspiratory flows has been made[19]. Constant flow rate magnitudes had mean values of corresponding cyclic patterns. Monodisperse aerosols had MMADs between about 3 μm and 8 μm. Deposition efficiencies at bifurcations and airways were greater in each generation for cyclic flows, and differences between cyclic and constant flows were greater for the smaller particles tested. The degree of enhancement within a bifurcation zone at the airstream divider (or carinal ridge), however, was observed to be greater for the corresponding constant flows.

Few experimental data are available concerning the deposition efficiencies of particulate matter in the human TB tree during exhalation. A dual hollow replica cast system was developed by Schlesinger *et al*[20] to study this problem. The major findings of this investigation relative to inspiratory studies were: (1) deposition during exhalation was less efficient than inhalation, and (2) during exhalation, deposition is enhanced for several centimetres in the trachea downstream to the main bronchi to trachea bifurcation, and in the main bronchi downstream to the lobar to main bronchial bifurcations. Particle deposition, apparently, is enhanced 'downstream' to airway branching sites during both inhalation and exhalation.

In summary, data from aerosol (polydisperse or monodisperse, submicron or large) deposition experiments in replica TB casts or models, for either constant or cyclic flows, during the inspiratory or expiratory phase of a simulated breathing pattern, indicate that aerosols may be very non-uniformly dispersed along respiratory passages. Information in the open literature, however, is mostly limited to large airway casts or models where deposition at bifurcations was maximum entering segmental (generation 3) bronchi, and usually declined in distal airways. Because of fluid dynamics considerations (i.e. a transition to laminar flow in peripheral bronchioles) and concomitant effects upon the relative efficiencies of dominant deposition mechanisms in TB airways (inertial impaction, sedimentation, diffusion), it might have seemed reasonable to assume, *a priori*, that the degree of bifurcation enhancement would probably decrease with progression through the human TB tree *in vivo*. It must be noted, however, that inhalation exposure tests have detected enhanced deposition patterns of both fibrous (asbestos, glass) and non-fibrous (ash, quartz), particles at the level of alveolar duct bifurcations in laboratory rats and mice[21,22].

The experimental data discussed above clearly indicate that the distribution of deposited aerosol mass within airways of a given generation is not homogeneous. This non-uniformity of dispersion suggests that considering the TB tree as a succession of 'bifurcation units' may be appropriate for studies of factors affecting the fate of inhaled particles of health effects concern. Therefore, regarding morphological measurements of airway parameters,

emphasis should be placed upon defining spatial airway orientation (branching angle, gravity angle) and anatomical features of airway branching sites (carinal geometry, surface irregularities, etc.).

IMPLICATIONS FOR DOSIMETRY

Inhaled cigarette smoke and naturally occurring radionuclides have been implicated in causal relationships with lung carcinomas[2,23]. *Site-selectivity* is an interesting feature of bronchogenic tumour development. Since bronchogenic carcinomas are usually detected in an advanced state, their sites of origin are often difficult to determine. Clinical studies indicate that large airways are preferential sites of tumour development[4,24-26], although predictive models suggest that submicron sized particles would be deposited primarily in more peripheral airways[27,28].

In a study of human lung tissue specimens from deceased smokers, highly concentrated deposits of an alpha-emitting isotope of polonium (^{210}Po) were found in large airway bifurcation zone epithelium[29]. Earlier histological studies had noted highly localised lesions (pre-neoplastic and neoplastic) at airway bifurcations[30,31]. The experimental findings[16,17] which imply that cigarette smoke particles may be initially deposited within upper airways of the lung *in vivo* support the hypothesis that epithelial cells at carinal ridges may receive much higher radiation doses (about one order of magnitude or even more) compared with cells located along tubular airway segments. Coupled with the relatively slower mucociliary action at airway branching sites[32,33], and the possibility of impaired clearance due to reduced mucous secretion and ciliary action by atmospheric irritants[34], the maldistribution of deposited cigarette smoke may result in increased exposure to radiation of bifurcation epithelial cells, thereby producing the documented site-selectivity of lung carcinomas.

Radionuclides attached to naturally occurring aerosols with activity median diameters (AMDs) ranging from 0.08 μm to 0.3 μm produce radiation doses in lung cells which exceed by far all other components of the natural radiation environment[35]. Fractionation in burning cigarettes may give rise to the association of radon progeny with particles in the 0.1-1.0 μm range in mainstream cigarette smoke, significantly increasing the AMDs[3]. The aetiology of lung cancer may be affected by synergistic interactions of indoor smoking. High alpha activities within 'hot spots' at bronchial bifurcations have been quantified in smokers exposed to average radon progeny levels within dwellings[3,36]. Perhaps the high incidence of lung cancer within large airways of smokers can be ascribed to the additive radiation dose, especially at segmental bifurcations (see Tables 1, 2, and 3), resulting from the deposition and accumulation of the following: mainstream cigarette smoke radon progeny aerosols, insoluble ^{210}Po-enriched particles created by combustion of tobacco trichomes, and natural radon progeny aerosols occurring indoors. In the uranium mining and milling industry, additional radiation problems for workers are caused by the inhalation of radium and uranium attached to dust particles in the micrometre range.

Data on the site of origin of lung cancers in underground miners[2,37] for smokers and non-smokers exposed to high levels of radon daughters indicate little difference in site prevalence between radiogenic and non-radiogenic lung cancers[22,38]. This finding is at variance with the calculated dose distribution throughout the bronchial tree[39,40]. The International Commission on Radiological Protection[41] suggested that bronchial epithelium basal cells be regarded as the sensitive target for lung cancer induction. The relevant dose for bronchial tumours, therefore, is the basal cell dose based on an airway-generation-specific mean surface activity. Experimentally observed heterogeneous deposition patterns in bronchial airways (particularly enhanced deposition at bifurcations) were not considered. Evidence exists that lung cancer risk may be more aptly related to local basal cell dose delivered to airway branching sites. As noted previously, bronchial tumours have been found mainly between generations 1 and 6, although the basal cell dose distribution is relatively uniform throughout the bronchial tree. It is in this region where the highest bifurcation deposition enhancement factors have been measured.

There may be, however, a paradoxical effect of cigarette smoke on concurrent exposure to radon decay products. Epidemiological data on uranium miners[42] and experimental data on beagle dogs[43] indicate that simultaneous smoking had a mitigating effect on radiation-induced lung cancers. This protective role of cigarette smoking might be due to: (1) a stimulatory effect on mucociliary clearance, or (2) an increased mucus production providing a shield of underlying sensitive cells. Such possible mechanisms might reduce the lung cancer incidence but do not, however, affect our arguments on the site selectivity of bronchial tumours in relation to nuclide accumulations at bifurcations relative to tubular airway segments.

Furthermore, Hofmann and Katz[44] have suggested that lung cancer induction in uranium miners requires two alpha particle hits in bronchial epithelial cells to match the epidemiologically observed lung cancer rate versus cumulative exposure function. Because of the enhanced activity concentration around the carinal ridge, the highest probability for multiple alpha particle hits occurs at

upper bronchial bifurcations. Finally, in a two-stage carcinogenesis model, we may identify the 'initiation event' as non-lethal alpha particle hits in basal cell nuclei leading to malignant transformation; the subsequently needed 'promotion event' may then be either stimulation of the mitotic activity of the basal cells by the killing of the fully differentiated epithelial cells ('radiological promotion') or synergistic action of other agents ('non-radiological promotion')[39]. Both the epithelial cell doses, as well as the surface concentrations of synergistically acting agents, peak at upper bronchial bifurcations[3,40].

The postulated increased carcinogenic efficiency of 'hot particles' as compared with a uniform dose distribution has been discussed[45]. Experimental data clearly show that 'hot particles' are less carcinogenic than uniformly distributed alpha-emitting radionuclides. The main reason for this finding is increased cell killing by multiple alpha particle traversals in a small tissue volume. In the case of 'hot spots' at bronchial branching sites the number of emitted alpha particles per unit time is significantly smaller than for 'hot particles', which makes multiple cellular hits a very unlikely event. Enhanced deposition increases only the number of cells traversed without increasing significantly the number of multiple cellular hits. Thus, the probability for cancer induction will also rise.

This report has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. This work was sponsored by EPA Contract No. 68-02-2566.

REFERENCES

1. Saccomanno, G., Archer, V. E., Saunders, R. P., James, L. A. and Beckler, P. A. *Lung Cancer of Uranium Miners on the Colorado Plateau.* Health Phys. **10**, 1195-1201 (1964).
2. Wagoner, J. K., Archer, V. E., Lundin, F. E. Jr, Holaday, D. A. and Lloyd, J. W. *Radiation as the Cause of Lung Cancer Among Uranium Miners.* New Engl. J. Med. **278**, 181-188 (1965).
3. Martell, E. A. *Alpha Radiation Dose at Bronchial Bifurcations of Smokers from Indoor Exposure to Radon Progeny.* Proc. Natl. Acad. Sci. **80**, 1285-1289 (1983).
4. Garland, L. H., Beier, R. L., Coulson, W., Heald, J. H. and Stein, R. L. *The Apparent Sites of Origin of Carcinomas of the Lung.* Radiology **78**, 1-11 (1962).
5. Owen, P. R. *Turbulent Flow and Particle Deposition in the Trachea.* IN CIBA Symposium on Circulatory and Respiratory Mass Transport, pp. 236-252 (London: Churchill) (1969).
6. Chan, T. L., Lippmann, M., Cohen, V. R. and Schlesinger, R. B. *Effect of Electrostatic Charges on Particle Deposition in a Hollow Cast of the Human Larynx-Tracheobronchial Tree.* J. Aerosol Sci. **9**, 463-468 (1978).
7. Chan, T. L., Schreck, R. M. and Lippmann, M. *Effect of the Laryngeal Jet on Particle Deposition in the Human Trachea and Upper Bronchial Airways.* J. Aerosol Sci. **11**, 447-459(1980).
8. Lippmann, M. and Altshuler, B. *Regional Deposition of Aerosol.* IN Air Pollution and the Lung, eds E. F. Aharonson, A. Ben-David and M. A. Klingberg, pp. 25-48 (New York: John Wiley) (1976).
9. Schlesinger, R. B., Cohen, V. R. and Lippmann, M. *Studies of Intrabronchial Particle Deposition Using Hollow Bronchial Casts.* IN Experimental Lung Cancer: Carcinogenesis and Bioassays, eds E. Karbe and J. F. Park, pp. 116-127 (New York: Springer Verlag) (1974).
10. Schlesinger, R. B., Bohning, D. E., Chan, T. L. and Lippmann, M. *Particle Deposition in a Hollow Cast of the Human Tracheobronchial Tree.* J. Aerosol Sci. **8**, 429-445 (1977).
11. Schlesinger, R. B. and Lippmann, M. *Selective Particle Deposition and Bronchogenic Carcinoma.* Environ. Res. **15**, 424-431 (1978).
12. Martonen, T. B. *Measurement of Particle Dose Distribution in a Model of a Human Larynx and Tracheobronchial Tree.* J. Aerosol Sci. **14**, 11-22 (1983).
13. Martonen, T. B. and Lowe, J. *Assessment of Aerosol Deposition Patterns in Human Respiratory Tract Casts.* IN Aerosols in the Mining and Industrial Work Environments, eds V. A. Marple and B. Y. H. Liu, Vol. 1, pp. 151-164 (Ann Arbor: Ann Arbor Science Publishers) (1983).
14. Chamberlain, A. C. and Dyson, E. D. *The Dose to the Trachea and Bronchi from the Decay Products of Radon and Thoron.* Br. J. Radiol. **29**, 317-325 (1956).
15. Landahl, H. D. *Particle Removal by the Respiratory System. Note on the Removal of Airborne Particulates by the Human Respiratory Tract with Particular Reference to the Role of Diffusion.* Bull. Math. Biophys. **25**, 29-30 (1963).
16. Martin, D. and Jacobi, W. *Diffusion Deposition of Small-Sized Particles in the Bronchial Tree.* Health Phys. **23**, 23-29 (1972).
17. Martonen, T. B., Hofmann, W. and Lowe, J. E. *Cigarette Smoke and Lung Cancer.* Health Phys. (In press).

18. Keith, C. H. and Derrick, J. C. *Measurement of the Particle Size Distribution and Concentration of Cigarette Smoke by the Conifuge*. J. Colloid. Sci. **15**, 340-356 (1960).
19. Schlesinger, R. B., Gurman, J. L. and Lippmann, M. *Particle Deposition Within Bronchial Airways: Comparisons Using Constant and Cyclic Inspiratory Flows*. IN Inhaled Particles, V, ed W. H. Walton, pp. 47-64 (Oxford: Pergamon Press) (1982).
20. Schlesinger, R. B., Concato, J. and Lippmann, M. *Particle Deposition During Exhalation: A Study in Replicate Casts of the Human Upper Tracheobronchial Tree*. IN Aerosols in the Mining and Industrial Work Environments, eds V. A. Marple and B. Y. H. Liu, Vol. 1, pp. 165-176 (Ann Arbor: Ann Arbor Science Publishers) (1983).
21. Brody, A. R., Hill, L. H., Adkins, B. Jr and O'Connor, R. W. *Chrysotile Asbestos Inhalation in Rats: Deposition Pattern and Reaction of Alveolar Epithelium and Pulmonary Macrophages*. Am. Rev. Respir. Dis. **123**, 670-679 (1981).
22. Brody, A. R. and Roe, M. W. *Deposition Pattern of Inorganic Particles at the Alveolar Level in the Lungs of Rats and Mice*. Am. Rev. Respir. Dis. **128**, 724-729 (1983).
23. Ochsner, A., Ochsner, A. Jr, H'Doubler, C. and Blalock, J. *Bronchogenic Carcinoma*. Dis. Chest **37**, 1-12 (1960).
24. Bryson, C. C. and Spencer, H. *Carcinoma of the Bronchus*. Q. J. Med. **20**, 173-186 (1951).
25. Herman, D. L. and Crittenden, M. *Distribution of Primary Lung Carcinomas in Relation to Time as Determined by Histochemical Techniques*. J. Natl. Cancer Inst. **27**, 1227-1271 (1961).
26. Garland, L. H. *Bronchial Carcinoma. Lobar Distribution of Lesions in 250 Cases*. Calif. Med. **95**, 7-8 (1961).
27. Task Group on Lung Dynamics. *Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract*. Health Phys. **12**, 173-207 (1966).
28. Lippmann, M. and Albert, R. E. *The Effect of Particle Size on the Regional Deposition of Inhaled Aerosols in the Human Respiratory Tract*. Am. Ind. Hyg. Soc. J. **30**, 257-275 (1969).
29. Little, J. B., Radford, E. P. Jr, McCombs, H. L. and Hunt, V. R. *Distribution of Polonium in Pulmonary Tissues of Cigarette Smokers*. New Engl. J. Med. **273**, 1343-1351 (1965).
30. Kotin, P. and Falk, H. L. *The Role and Action of Environmental Agents in the Pathogenesis of Lung Cancer. I. Air Pollutants*. Cancer **12**, 147-163 (1959).
31. Auerbach, O., Stout, A. P., Hammond, E. C. and Garfinkel, L. *Changes in Bronchial Epithelium in Relation to Cigarette Smoking and in Relation to Cancer*. New Engl. J. Med. **265**, 253-267 (1961).
32. Macklin, C. C. *Induction of Bronchial Cancers by Local Massing of Carcinogen in Outdrifting Mucus*. J. Thorac. Surg. **31**, 238-244 (1956).
33. Hilding, A. C. *Ciliary Streaming in the Bronchial Tree and the Time Element in Carcinogenesis*. New Engl. J. Med. **256**, 634-640 (1957).
34. Lippmann, M. *Regional Deposition of Particles in the Human Respiratory Tract*. IN Handbook of Physiology: Reaction to Environmental Agents, ed D. H. K. Lee, pp. 213-232 (Baltimore: American Physiological Society) (1977).
35. Pohl, E., Steinhäusler, F., Hofmann, W. and Pohl-Rüling, J. *Methodology of Measurements and Statistical Evaluation of Radiation Burden to Various Population Groups from all Internal and External Natural Sources*. IN Biological and Environmental Effects of Low-Level Radiation, STI/PUB/409, Vol. II, pp. 305-315 (Vienna: IAEA) (1976).
36. Martell, E. A. and Sweder, K. S. *Properties of Radon Progeny Aerosols in Mainstream Cigarette Smoke and the Alpha Dose at Segmental Bifurcations of Smokers*. IN Current Concepts in Lung Dosimetry, ed D. R. Fisher. Battelle Pacific Northwest Laboratories, PNL-SA-11049, pp. 144-151 (1983).
37. deVilliers, A. G. and Windish, J. P. *Lung Cancer in a Fluorspar Mining Community. I. Radiation, Dust, and Mortality Experience*. Br. J. Ind. Med. **21**, 94-109 (1964).
38. Rosenblatt, M. B. and Lisa, J. R. *Cancer of the Lung – Pathology, Diagnosis and Treatment*. (Oxford University Press) (1956).
39. Hofmann, W. *Lung Cancer Induction by Inhaled Radon Daughters – What is the Relevant Dose?* Radiat. Prot. Dosim. **7**, 367-370 (1984).
40. Hofmann, W. *Cellular Lung Dosimetry for Inhaled Radon Decay Products as a Base for Radiation-Induced Lung Cancer Risk Assessment. I. Calculation of Mean Cellular Doses*. Radiat. Environ. Biophys. **20**, 95-112 (1982).
41. International Commission on Radiological Protection. *Limits for Inhalation of Radon Daughters by Workers*. ICRP Publication 32. Ann. ICRP **6** (Oxford: Pergamon Press) (1981).
42. National Council on Radiation Protection and Measurements. *Evaluation of Occupational and Environmental Exposures to Radon and Radon Daughters in the United States*. NCRP Report No. 78 (Bethesda, MD: NCRP Publications) (1984).
43. Cross, F. T., Palmer, R. F., Filipy, R. E., Dagle, G. E. and Stuart, B. O. *Carcinogenic Effects of Radon Daughters, Uranium Ore Dust and Cigarette Smoke in Beagle Dogs*. Health Phys. **42**, 33-52 (1982).
44. Hofmann, W. and Katz, R. *Track Structure Analysis of Radiation Carcinogenesis at Low Doses*. IN Proc. 8th Symp on Microdosimetry, eds J. Booz and H. G. Ebert, EUR 8393, pp. 565-573 (Luxembourg: Commission of the European Communities) (1983).
45. Fisher, D. R. and Frazier, M. E. *The "Hot Particle" Controversy: New Answers to Old Questions*. Presented at the 28th Annual Meeting of the Health Physics Society, Baltimore, MD, USA (1983).